LIFC
Lega Italiana
Fibrosi Cistica

European Medicines Agency - EMA -CHMP

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Object: Extension of the authorization for Kaftrio and Kalydeco

Dear CHMP Chair and vice-Chair,

We are writing to you as the Lega Italiana Fibrosi Cistica (LIFC), a national association that has supported and represented every person affected by Cystic Fibrosis (CF) for over 40 years, in collaboration with its twenty regional branches and territorial CF Care Centers. Our commitment is to ensure the improvement of available treatments and the recognition of social rights, in order to comprehensively improve the patients' quality of life.

This letter aims to contribute to your evaluation regarding the extension of Kaftrio and Kalydeco (elexacaftor/tezacaftor/ivacaftor or ETI) to people suffering from CF who do not currently meet the criteria for the prescription of these drugs. We specifically urge the extension to individuals with rare responsive CFTR gene mutations based on clinical and/or *in vitro* data. The French study by PR Burgel (1) demonstrated clinical efficacy of the drug in terms of reducing sweat chloride values, improving respiratory function, and suspension from the lung transplant list, even in subjects with mutations other than those for which ETI is approved.As Italians, we feel particularly involved in this phase since the data from our national disease registry (Italian Cystic Fibrosis Registry) show a high percentage of subjects with genotypes not eligible for ETI therapy under the current prescription criteria. Only 67.91% of Italian CF subjects bear at least one F508del allele (2), while an additional 12.44% could benefit from the expansion of ETI prescribing to subjects with the mutations approved by the FDA. Moreover, data from the European Registry indicate that fewer than 80% of adults are eligible and treated with ETI in Italy, unlike other Western European countries, which have percentages close to 90%. (3)

Therefore, we believe it is crucial to actively engage in requesting a rapid and hopefully positive evaluation of the requested extension. It is urgent to provide a concrete answer to the many Italian patients we represent, who cannot hope in improvements in their clinical conditions and, unfortunately, are witnessing their progressive worsening.

Significant clinical results have been documented in some patients through the provision of the drug in the "off-label" or "compassionate" modalities. The costs of this approach have been borne by healthcare facilities, a choice that requires extensive approval time considering the high cost of the drugs, and which not all regional structures can support.
We also remind that in our country, the second most frequent variant of the CFTR gene is the N1303K mutation, present in more than 10% of Italian patients (2). A French study on the compassionate use of ETI, concerning subjects with N1303K and other CFTR mutations, demonstrated a clinical benefit in almost half of them. (4)
Furthermore, *in vitro* tests on cells (from nasal mucosa) or organoids (obtained by rectal biopsy) from patients with genotypes not eligible for ETI therapy showed a positive response, raising the question of a possible clinical response in these subjects as well. (5)
In support of our request, we provide the testimony of the CF Regional Center of the Veneto Region on the effects of off-label therapy with ETI in 15 subjects with rare CF variants non yet approved for the use of ETI:

"Regarding real data on the use of ETI in CF patients, followed at the CF Center in Verona with rare CF mutations non yet approved for the use of triple therapy, we reported below data of 15 patients who received ETI treatment with an off-label prescription.
Fifteen CF patients (8 M), age range 13-59 years, received treatment with ETI. Eight carried the N1303K mutation in one allele, 3 carried the 3849+10kbC→T mutation in one allele, one the G85E mutation in one allele and one the 2789+5G>A mutation in one allele. All these mutations are recognized as responders to ETI from literature and are under evaluation by EMA for approval.
The other two patients carried A559T/A559T and W57G/A234D mutations, respectively.
All patients showed an improvement in their quality of life, in particular with a reduction in the respiratory symptoms, a reduction in the number of infections, a mean increase in the respiratory function with FEV1 +10 pp (range 0-38 pp) respect to baseline.
No evidence was registered in the change of the hepatic enzyme levels after at least one year of follow up. An improvement in the CFQR test was also recorded before and after one year of treatment.
A significant increase of the nutritional status was also found with an increase of BMI from 20.65 to 21.68 after one year of treatment."

These data are not intended to represent absolute data or to have rigorous scientific character but simply to share the method used by Italian healthcare facilities. The approach used in territorial Care Centers has combined scientific rigor, demonstrated by the choice to treat with ETI after in vitro evidence of a positive response from the patients' cells, and to closely monitor the patient's clinical response, with the empathy necessary for the physician in clinical situations where no other solutions are available to support the patient's life (compassionate treatments).

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We also remind that in our country, in addition to the subjects with a genotype composed of two minimal function CFTR variants who cannot access therapy with CFTR modulators, (10% of our total population), the remaining part of patients who cannot yet benefit from ETI therapy is mainly consist of those with genotypes characterized by rare CFTR variants. This makes the planning and execution of the classic three-phase clinical trials practically impossible. Therefore, we believe that the possibility of the requested extension already positively amplifies the expected clinical response. At the same time, we hope that further reflections may lead to the possibility of authorizing the use of the ETI starting from "real-world data" when clinical conditions are particularly desperate, together with the evaluation of the "real evidence" on the most significant outcomes for assessing of the clinical conditions of CF patients.

As an association representing patients and their families, we consider ourselves "expert stakeholders," and are well aware that the extension of ETI prescriptions we are requesting (desirable from our point of view and feasible exclusively through rigorous and timely subsequent clinical evaluation procedures) can be better assessed between your Committee and European CF scientific experts. However, we believe it is important to encourage reflection on this issue by reminding that, as one of our patients said, the "clock of a CF patient's time runs significantly faster" than the clock of a healthy person.

Thank you for your kind attention. We remain at your disposal for any further comments or information.

Best regards,

Giovanna Puppo Fornaro
President

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